Citation:

Wang X, Qin X, Demirtas H, Li J, Mao G, Huo Y, Sun N, Liu L, Xu X. Efficacy of folic acid supplementation in stroke prevention: A meta-analysis. *Lancet*. 2007; 369 (9,576): 1,876-1,882.

PubMed ID: 17544768

Study Design:

Meta-analysis

Class:

M - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To do a meta-analysis focusing on stroke as the disease endpoint in relation to folic acid supplementation.

Inclusion Criteria:

- Medline database search (January 1966 to July 2006) with the MeSH terms “cardiovascular disease,” “coronary disease,” “coronary thrombosis,” “myocardial ischemia,” “coronary stenosis,” “coronary restenosis,” “cerebrovascular accident,” “randomized controlled trial,” “clinical trials” and “folic acid,” and the text words “folic acid” and “folate”
- Medline search was done with the same methods, with the addition of “stroke” and “multivitamins” as text words and extension of the search period to April 2007
- Manual searches of bibliographies of all relevant trials and review articles
- The search was restricted to human studies. There were no language restrictions
- Studies were eligible for inclusion if:
    - The study was a randomized controlled trial
    - The number of events for stroke that occurred during the study were reported by intervention and control groups, with more than ten incident cases
    - The intervention consisted of folic acid supplementation (with or without additional B vitamin supplementation)
    - The intervention duration was at least six months
- The contents of 308 abstracts were reviewed independently by two investigators to determine if they met eligibility criteria for inclusion. Where discrepancies occurred, a third investigator did additional assessment.

Exclusion Criteria:

- 293 studies were excluded by review of abstract (not randomized controlled trials, no cardiovascular disease outcomes, not including folic acid)

- Seven studies were excluded due to one duplicate report, five no stroke or cardiovascular endpoints reported, one small incident case.

Description of Study Protocol:

Recruitment

Using Medline, eight RCTs, consisting of 16,841 individuals.

Design

Meta-analysis.

Blinding Used

Two study were open and five studies were double-blind.

Intervention

Yes.

Statistical Analysis

- Data were stratified by duration of folic acid supplementation (36 months or less vs. more than 36 months); decrease in homocysteine concentration (less than 20% vs. 20% or more) and prior folic acid grain fortification (yes or no)
- Data were further stratified by history of stroke (yes or no) to assess the effect of folic acid supplementation on stroke risk in primary vs. secondary prevention
- Relative risk (RR) with 95% CI was used as a measure of the effect of folic acid supplementation on risk of stroke
- Unconditional maximum likelihood estimation by normal approximation was used to obtain the interval estimate of the RR of stroke for folic acid supplementation compared with controls
- To ensure the robustness of RR and 95% CI, they applied logarithmically transformed risk ratios, and calculated corresponding SE by the delta method and then back-transformed (exponential transformation) to the original scale. The results were very similar between the two methods so they only present the results for the untransformed version
- Both fixed-effects and random-effects models were used to calculate the pooled RR for folic acid supplementation compared with controls. Although both models yielded similar

findings, results from the random-effects models were presented because of the different pre-existing conditions, intervention regimens, intervention duration and dietary intakes of folic acid involved in the original trials.
- Heterogeneity between studies was assessed by Cochran's Q with a significance level set at 0.10. Sensitivity analysis was completed by removing each individual trial from the meta-analysis. All the analyses were done with R software, version 2.4.1
- For studies in which more than one folic acid intervention regimen existed, they reported the mean concentration of
homocysteine both before and after the intervention for all the intervention groups combined. For these studies, they combined the number of events and participants across folic acid intervention groups to obtain a single event rate for folic acid supplementation.

Data Collection Summary:

- *Timing of measurements:* January 1966 to July 2006
- *Dependent variables:* Stroke events
- *Independent variables:* Group (intervention vs. control): Folic acid supplementation with or without B, or in combination with other B vitamins, including B_6 and B_{12}.

Description of Actual Data Sample:

- *Attrition:* N=16,841
- *Age:* Mean age of the studies' participants ranged between 56 and 68.9 years
- *Other relevant demographics:*
    - All studies had participants with pre-existing conditions:
        - Stoke
        - Coronary heart disease
        - End stage renal disease
        - Oesophageal dysplasia
    - Baseline homocysteine concentrations ranged from 12.1 to 35.0mmol per L
    - Three trials were done in regions with grain fortification, four were in regions without grain fortification and one in a population from both fortified and non-fortified regions
- *Location:*
    - Three studies were from US and Canada
    - Three studies were from European countries
    - One from Australia and New Zealand
    - One from China.

Summary of Results:

- Pooling all eight trials, folic acid supplementation (with or without other B vitamins) significantly reduced
the risk of stroke by 18% (RR 0.82, 95% CI 0.68 to 1.00; P=0.045). Heterogeneity testing for all analyses
in table 3 showed that all P values are larger than 0.10; thus heterogeneity was not

significant in the overall analysis and in stratified analyses. Sensitivity analyses showed that the RR and 95% CI did not alter substantially by removing any one trial

- Longer intervention duration seemed to be associated with greater reduction in the RR of stroke. When the data were stratified by intervention duration (36 months or less vs. more than 36 months), the pooled RR for the trials with shorter duration was 1.00 (95% CI 0.83 to 1.21; P=0.95); by contrast the pooled RR for the trials with longer duration was 0.71 (0.57 to 0.87; P=0·001)
- When the data were stratified by fortification status, the RR for trials in regions with fortified grain was 0.89 (95% CI 0.55 to 1.42; P=0.62); that for trials in regions without fortification was 0.75 (0.62 to 0.91; P=0.003). When the data was stratified by history of stroke, the RR for the trial in which there was a history of stroke was 1.04 (0.84 to 1.29; P=0.71); the RR for trials with no such history was 0.75 (0.62 to 0.94; P=0.002).

Table 3 (in the paper): **Pooled Relative Risk for Stroke, Stratified by Intervention Duration, Percentage Change in Homocysteine Concentration, Grain Fortification and History of Stroke**

	Stroke Events/Total Patients	Stroke Events/Total Patients	Relative Risk (95% CI)	P-value
	Intervention Group	Control Group		
Overall	373/8,949	405/7,892	0.82 (0.68-1.00)	0.045
Duration of intervention				
36 months or less	224/4,078	193/3,015	1.00 (0.83-1.21)	0.95
36 months or more	149/4,871	212/4,877	0.71 (0.57-0.87)	0.001
Homocysteine lowering				
20% or less	19/2,325	174/2,180	0.89 (0.55-1.42)	0.62
More than 20%	172/4,967	196/4,051	0.77 (0.63-0.94)	0.012
Grain fortification				
Yes	179/2,325	14/2,180	0.89 (0.55-1.42)	0.62
No	194/6,624	231/5,712	0.75 (0.62-0.91)	0.003
History of stroke				
Yes	152/1,827	148/1,853	1.04 (0.84-1.29)	0.71
No	221/7,122	257/6,039	0.75 (0.62-0.90)	0.002

- Post-intervention homocysteine reduction was measured in all but one trial (table 4). There seemed to be an inverse relation between degree of homocysteine lowering and RR of stroke
- When the data was stratified by the degree of homocysteine lowering, the RR for the trials with a reduction in homocysteine concentration of less than 20% was 0.89 (95% CI 0.55 to 1.42; P=0.62); by contrast, the RR for the trials with a reduction in homocysteine concentration of 20% or more was 0.77 (0.63 to 0.94, P=0.012; table 3).

Table 4 (in the paper) **Relative Risk of Stroke and Change in Homocysteine Concentration**

	Net Decrease in Homocysteine (mmol per L)	Change in Homocysteine (%)	Stroke Events/Total Participants	Stroke Events/Total Participants	RR (95% CI)
			Intervention	Control	
Toole, et al	-2.3	-17.2%	152/1,827	148/1,853	1.04 (0.84-1.29)
Liem, et al	-2.6	-21.5	8/300	12/293	0.6 (0.27-1.57)
Lonn, et al	-3.2	-26.2	111/2,758	147/2,764	0.76 (0.59-0.96)
Conaa, et al	-3.8	-29.0	49/1,872	27/943	0.91 (0.58-1.45)
Zoungas, et al	-4.7	-17.4	8/156	18/159	0.45 (0.20-1.01)
Wrone, et al	-3.6	-10.9	19/342	8/168	1.17 (0.52-2.61)
Righetti, et al	-15.1	-39.4	4/37	10/51	0.55 (0.19-1.62)
Mark, et al	NR	NR	22/1,657	35/1,661	0.63 (0.37-1.07)

NR= not reported.

- Toole JF, Malinow MR, Chambless LE, et al. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: The Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. *JAMA.* 2004; 291: 565-575.
- Liem A, Reynierse-Buitenwerf GH, Zwinderman AH, et al. Secondary prevention with folic acid: Results of the Goes extension study. *Heart.* 2005; 91: 1,213-1,214.
- Lonn E, Yusuf S, Arnold MJ, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med.* 2006; 354: 1,567-1,577.
- Bonaa KH, Njolstad I, Ueland PM, et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N Engl J Med.* 2006; 354: 1,578–1,588.
- Zoungas S, McGrath BP, Branley P, et al. Cardiovascular morbidity and mortality in the Atherosclerosis and Folic Acid Supplementation Trial (ASFAST) in chronic renal failure: A multicenter, randomized, controlled trial. *J Am Coll Cardiol.* 2006; 47: 1,108-1,116.
- Wrone EM, Hornberger JM, Zehnder JL, et al. Randomized trial of folic acid for prevention of cardiovascular events in end stage renal disease. *J Am Soc Nephrol.* 2004; 15: 420-426.
- Righetti M, Serbelloni P, Milani S, et al. Homocysteine-lowering vitamin B treatment decreases cardiovascular events in hemodialysis patients. *Blood Purif.* 2006; 24: 379-386.
- Mark SD, Wang W, Fraumeni JF Jr, et al. Lowered risks of hypertension and cerebrovascular disease after vitamin/mineral supplementation: The Linxian Nutrition Intervention. *Am J Epidemiol.* 1996; 143: 658-664.

Author Conclusion:

The meta-analysis provides coherent evidence that folic acid supplementation can significantly reduce the risk of stroke in primary prevention.

Reviewer Comments:

The authors noted the following limitations:

- *Meta-analyses have inherent limitations, including their retrospective and aggregate nature and the inability to adjust for individual variables*
- *There was no significant heterogeneity between studies*
- *The sample size of the trials included in this analysis varied, and the results were more likely affected by the trials with larger sample sizes*
- *Sensitivity testing and found that the RR and 95% CI did not alter substantially after removing any one trial*
- *Publication bias is an important issue for meta-analysis, in which positive results are more likely to be published, and as such, meta-analyses could overestimate the true effect or association. The primary endpoints were cardiovascular disease rather than stroke in most of the published trials, of which most studies reported a non-significant association with cardiovascular disease. Therefore, the publication bias, if any, will probably underestimate the effect of folic acid supplementation*
- *Since none of the included trials was designed exclusively for stroke, the effect of publication bias on the estimated effect of folic acid supplementation on stroke should be limited*
- *This meta-analysis is limited by the original study design of the trials and cannot assess the efficacy of single vs. combination regimen, nor on dosage*
- *The findings remain to be confirmed by data from several large trials that have yet to report results and should be interpreted in the context of available evidence in the field.*

Research Design and Implementation Criteria Checklist: Review Articles

Relevance Questions		
1.	Will the answer if true, have a direct bearing on the health of patients?	Yes
2.	Is the outcome or topic something that patients/clients/population groups would care about?	Yes
3.	Is the problem addressed in the review one that is relevant to nutrition or dietetics practice?	Yes
4.	Will the information, if true, require a change in practice?	Yes

Validity Questions		
1.	Was the question for the review clearly focused and appropriate?	Yes

2.	Was the search strategy used to locate relevant studies comprehensive? Were the databases searched and the search termsused described?	Yes
3.	Were explicit methods used to select studies to include in the review? Were inclusion/exclusion criteria specified and appropriate? Were selection methods unbiased?	Yes
4.	Was there an appraisal of the quality and validity of studies included in the review? Were appraisal methods specified, appropriate, and reproducible?	Yes
5.	Were specific treatments/interventions/exposures described? Were treatments similar enough to be combined?	Yes
6.	Was the outcome of interest clearly indicated? Were other potential harms and benefits considered?	Yes
7.	Were processes for data abstraction, synthesis, and analysis described? Were they applied consistently across studies and groups? Was there appropriate use of qualitative and/or quantitative synthesis? Was variation in findings among studies analyzed? Were heterogeneity issued considered? If data from studies were aggregated for meta-analysis, was the procedure described?	Yes
8.	Are the results clearly presented in narrative and/or quantitative terms? If summary statistics are used, are levels of significance and/or confidence intervals included?	Yes
9.	Are conclusions supported by results with biases and limitations taken into consideration? Are limitations of the review identified and discussed?	Yes
10.	Was bias due to the review's funding or sponsorship unlikely?	Yes